Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Chen Y. et al. (2012) Meta-analysis: IL28B polymorphisms predict sustained viral response in HCV patients treated with pegylated interferon-alpha and ribavirin. *Alimentary Pharmacology & Therapeutics*, 36(2):91-103
Date of Review:	March 10, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **Peg-IFN α/ribavirin-treated HCV patients** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **China** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; determine IL28B rs12979860 CC and rs8099917 TT genotypes' correlation with sustained virological response in hepatitis C patients treated with Peg-IFN alpha/ribavirin
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Article mentioned that for genotype 1-infected patients, tests for IL28B rs12979860 or rs8099917 polymorphisms can help guide physicians in treatment regimen and design and/or the patient's decision to undergo therapy
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the	☒	☐	☐	

results?				
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	Similar analysis could be done
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Free access from http://onlinelibrary.wiley.com
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☒	☐	☐	This study was funded in full by the Major National Science and Technology Projects for Infectious Diseases (11th Five-Year Plan, China), the National Natural Science Fund of China and Jiangsu Health International Exchange Program sponsorship
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	Limitations: - Only published studies were included, which may have lead to publication bias - Small sample size for genotype 2/3 and genotype 4 groups - Methodological deficiencies of included studies - Non-genetic factors may influence SVR of antiviral-treated

				HCV patients
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☒	☐	Included relevant articles published up to October 15, 2011
Are these data regularly collected at and/or below a national level?	☐	☒	☐	
Are these data collected manually or electronically?	☐	☐	☐	Electronically: use of PubMed, Web of Science, Embase and the Chinese BioMedical Literature databases
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Alimentary Pharmacology & Therapeutics*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Utilize existing data/surveillance information: 25 published studies included

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: IL28B polymorphisms predict sustained viral response in HCV patients treated with pegylated interferon-α and ribavirin

Y. Chen*,†, H.-X. Xu†,‡, L.-J. Wang‡, X.-X. Liu†, R. I. Mahato§ & Y.-R. Zhao*

*Department of Infectious Diseases, First Affiliated Hospital of the Medical College of Xi'an Jiaotong University, Xi'an, Shanxi Province, China.
†Institute of Liver Diseases, Huai'an Fourth People's Hospital, Huai'an, China.
‡Department of Infectious Diseases, Affiliated Hospital of the Xuzhou Medical College, Xuzhou, China.
§Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN, USA.

Correspondence to:
Dr Y.-R. Zhao, Department of Infectious Diseases, First Affiliated Hospital of the Medical College of Xi'an Jiaotong University, No. 277 Yanta West Road, Xi'an 710061, Shanxi Province, China.
E-mail: zhaoyingren@sohu.com

Publication data
Submitted 11 January 2012
First decision 8 February 2012
Resubmitted 23 March 2012
Accepted 23 April 2012
EV Pub Online 16 May 2012

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr P. Collins.

SUMMARY

Background
Interleukin (IL) 28B single nucleotide polymorphisms can predict sustained virological response (SVR) in hepatitis C virus (HCV) patients following pegylated interferon-alpha (PEG IFN-α) and ribavirin treatment.

Aim
To design a meta-analysis to determine IL28B genotypes', rs12979860 CC and rs8099917 TT, correlation with SVR in PEG IFN-α/ribavirin-treated HCV patients.

Methods
Meta-analysis was performed in 17 studies of rs12979860 CC vs. CT/TT and 17 of rs8099917 TT vs. TG/GG. Odds ratios (OR) and confidence intervals (95% CI) were calculated by fixed- or random-effects models. Heterogeneity, sensitivity analysis and publication bias were also assessed.

Results
Of 4252 Asian, Caucasian and African HCV patients analysed for rs12979860, SVR was more frequent in CC (vs. CT/TT; OR = 4.76, 95% CI: 3.15–7.20). Moreover, CC was associated with SVR for HCV genotype-1 or -4 infections ($OR_{genotype\ 1}$ = 5.52, 95% CI: 3.74–8.15; $OR_{genotype\ 4}$ = 8.11, 95% CI: 4.13–15.93), regardless of ethnicity. Of 4549 Caucasian and Asian HCV patients analysed for rs8099917, SVR was more frequent in TT (vs. TG/GG; OR = 3.31, 95% CI: 2.39–4.59). Moreover, TT was associated with SVR for HCV-1 ($OR_{genotype\ 1}$ = 4.28, 95% CI: 2.87–6.38). Rs8099917 TT predictive value was stronger in Asians (OR_{Asians} = 8.09, 95% CI: 5.63–11.61; $OR_{Caucasians}$ = 3.00, 95% CI: 2.03–4.45). Ethnicity stratification revealed that rs8099917 TT had slight predictive value in Asian HCV-2/3 patients (OR = 1.99, 95% CI: 1.09–3.62).

Conclusions
IL28B rs12979860 CC and rs8099917 TT are strong SVR predictors for PEG IFN-α/ribavirin-treated HCV-1 patients, regardless of ethnicity. In HCV-2/3, rs12979860 CC has no SVR predictive value, but rs8099917 TT was slightly associated with SVR in Asians.

Aliment Pharmacol Ther 2012; **36**: 91–103

© 2012 Blackwell Publishing Ltd
doi:10.1111/j.1365-2036.2012.05131.x

INTRODUCTION

Hepatitis C virus (HCV) infection has reached epidemic proportions worldwide, with the number of chronically infected persons estimated at 200 million. The long-term hepatic impact of HCV infection can range from fibrosis to cirrhosis with or without hepatocellular carcinoma (HCC).[1] Currently, the standard therapy for chronic HCV infection is a combination regimen of pegylated interferon-alpha (PEG IFN-α) and ribavirin (RBV).[2] Patient response to therapy varies widely, and it is believed that genetic factors underlie this phenomenon. The primary goal of any HCV therapy is to achieve a sustained virological response (SVR), in which HCV RNA remains undetectable at 24 weeks after therapy ends. For PEG IFN-α/RBV, 40–50% of patients infected with HCV genotypes 1 or 4 attain SVR, whereas 70–90% of patients infected with genotypes 2 or 3 attain SVR.[3–8] Unfortunately, the combination therapy produces several serious side effects, such as a flu-like syndrome, haematological abnormalities and adverse neuropsychiatric events, which necessitate dose reduction. Between 10% and 14% of patients suffer such extensive effects that treatment termination is required.[9] Thus, it is important to identify patients who are ultimately going to be resistant to treatment, to avoid unnecessarily inducing detrimental side effects and to reduce the substantial cost of PEG-IFN-α/RBV treatment. Several studies to date have aimed to identify accurate and sensitive predictive biomarkers of treatment response. Besides virus genotype, several other factors related to the virus (e.g. viral load at treatment initiation) and host (e.g. race, age, body weight, insulin resistance, serum lipids, fibrosis stage, serum vitamin D concentration and treatment compliance) can influence antiviral-induced SVR in chronic HCV patients.[10–15]

Host genetic factors have been proposed as mediators of treatment response. Chronic HCV patients of European or Asian ancestry[6] have a higher rate of SVR than African ancestry patients,[16] reinforcing the theory of genetics as contributing to SVR risk. Previous studies have investigated many potential genetic factors, including polymorphisms of the human leucocyte antigens (HLA) and the interleukin (IL)10 promoter, but results have been inconsistent.[17, 18] Recently, several genome-wide association studies (GWAS) have indicated that single nucleotide polymorphisms (SNPs) near the interferon-gamma3-encoding IL28B gene may be associated with SVR after PEG-IFN-α/RBV therapy.[19–22] IL28B rs12979860 and rs8099917 have particularly strong linkage disequilibrium, and are considered as the most important predictive factors for treatment response. The rs12979860 CC genotype has a higher incidence of SVR than the CT/TT genotypes, and the rs8099917 TT genotype has higher SVR incidence than the TG/GG genotypes. However, the magnitude of the impact of rs12979860 and rs8099917 polymorphisms on treatment response remains controversial. Meta-analysis is a powerful method for quantitatively summarising the results from different studies. It is particularly useful when individual trials have insufficient statistical power, since pooling of trial subjects increases the sample size and decreases random error.

Therefore, we performed meta-analyses to determine the impact of IL28B rs12979860 genotype CC and rs8099917 genotype TT for chronic HCV patients infected with different virus genotypes and of different ethnicities.

METHODS

Literature search

The PubMed, Web of Science, Embase and the Chinese BioMedical Literature (CBM) databases were searched for relevant articles published up to October 15, 2011 using the following search terms: 'chronic hepatitis C', 'HCV', or 'hepatitis C virus'; 'interleukin-28B' or 'IL-28B'; 'polymorphism' or 'genetic polymorphism'; 'sustained virological response' or 'SVR'. To identify other relevant publications, the reference lists of all retrieved articles were manually searched; in addition, cited review articles were retrieved and perused for mention of any additional potentially relevant articles. Only published studies with full text articles were included in the meta-analysis. A flowchart of the study selection process is shown in Figure 1.

Inclusion and exclusion criteria

Studies were selected based on the following inclusion criteria: (a) HCV-infected patients received PEG-IFN-α/RBV combination therapy; (b) HCV genotype 1/4-infected patients received treatment for 48 weeks, and genotype 2/3-infected patients received treatment for 24 weeks; (c) SVR rates were compared with IL28B rs12979860 CC genotype and CT/TT genotype, or with rs8099917 TT genotype and TG/GG genotype; and (d) the genotype was tested to ensure the Hardy–Weinberg equilibrium (HWE). Studies were excluded according to the following criteria: (i) non-human population; (ii) co-infection with hepatitis B or human immunodeficiency virus HIV; (iii) co-existence of any other liver diseases, such as autoimmune hepatitis, alcoholic liver disease, drug hepatitis, Wilson's

© 2012 Blackwell Publishing Ltd

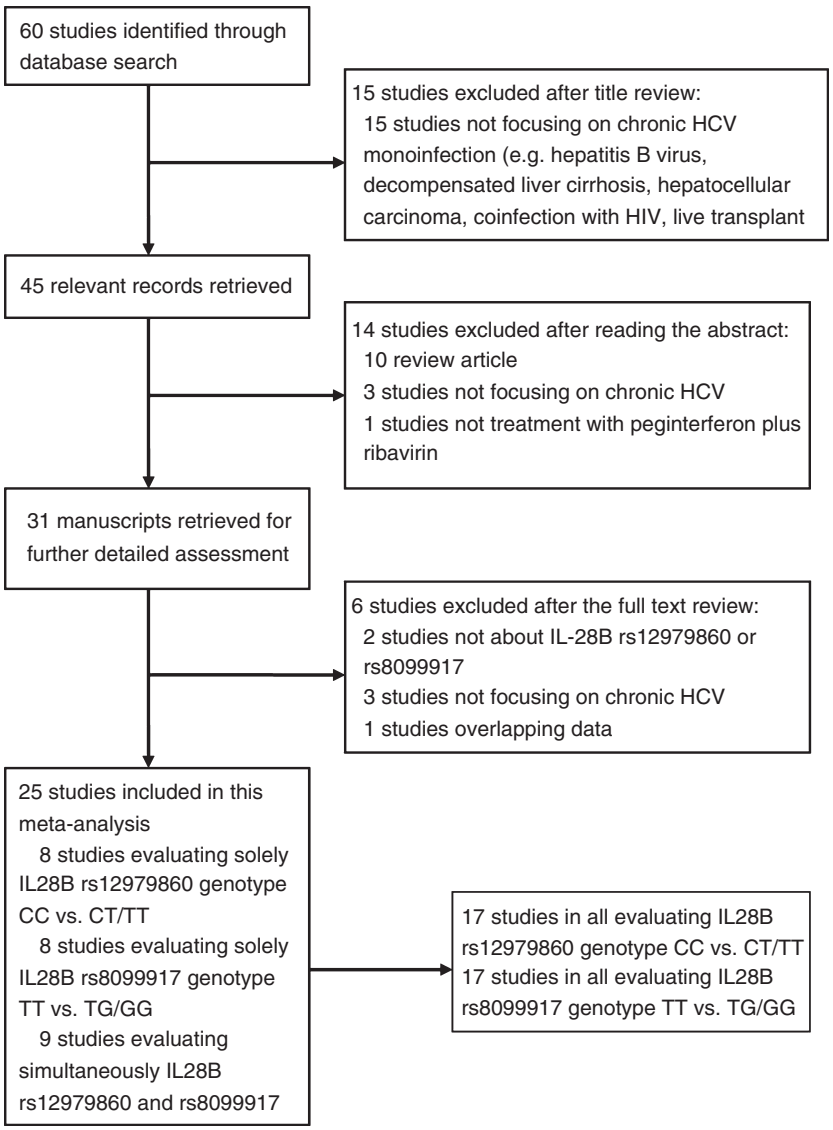

Figure 1 | Flowchart of the process for selecting studies for inclusion in the meta-analysis.

disease, decompensated liver cirrhosis or HCCs; (iv) liver transplantation recipients; (v) treatment with non-PEG IFN, or without RBV; (vi) study population deviated from HWE; or (vii) absent information on SVR rates in patients with IL28B SNPs rs12979860 CC vs. CT/TT or rs8099917 TT vs. TG/GG. When several publications reported data from a single study, the most recent and complete publication was selected.

Data extraction and study design

Data extraction was carried out by two independent investigators (Yong Chen and He-Xiang Xu) using predefined forms. All discrepancies were resolved by discussion, and, if required, participation by the third author (Ying-Ren Zhao). For all included studies, the following information was extracted: first author, publication year, ethnicity and geographical area, HCV genotype, number of chronic HCV cases, number of SVR cases, genotype frequency of IL28B in chronic HCV cases, genotype frequency of IL28B in SVR HCV cases. SVR was defined as undetectable HCV RNA at the end of treatment.

All meta-analyses were performed using the Review Manager (RevMan version 5.1; http://ims.cochrane.org/revman). The first overall analysis included all patients infected with HCV, regardless of virus genotype. The second analysis stratified patients by virus genotype. Since genotypes 2 and 3 require the same standard therapy time and attain similar SVR rates, these two genotypes were included in the same analysis. Within each of the genotype stratification analyses, additional

© 2012 Blackwell Publishing Ltd

stratification by ethnicity (Caucasian, Asian and African) was analysed.

Data analysis

Statistical analyses were performed using the Review Manager version 5.1 for Windows (Cochrane Collaboration, Oxford, UK) and Stata version 10.0 (Stata Corp LP, College Station, TX, USA) software programs. The association strength between IL28B SNPs (rs12979860 or rs8099917) and SVR in HCV patients treated with PEG-IFN-α/RBV was determined by calculating the respective odds ratio (OR) with 95% confidence intervals (CI). The significance of the pooled OR was determined by the *Z*-test, and a *P*-value of less than 0.05 was considered significant. Two meta-analysis models for dichotomous outcomes were used: the random-effects model (using DerSimonian and Laird's method[23]) and the fixed-effects model (using Mantel-Haenszel's method[24]). To assess between-study heterogeneity, both the Chi-squared based *Q* statistic test (Cochran's *Q* statistic) and the I^2 statistic[25] were calculated. For Cochran's *Q* statistic, heterogeneity was considered significant for $P < 0.10$ and the results were pooled by the random-effects model. When $P > 0.10$, the fixed-effects model was used. In addition, the Galbraith plot was used to detect potential sources of heterogeneity (outliers).[26] To validate the meta-analysis results, a sensitivity analysis was performed by sequential omission of individual studies or by omitting outlier studies identified by the Galbraith plotting method. Publication bias was investigated by funnel plot, Egger's linear regression method and Begg's rank correlation method.[27] All *P*-values were two-sided. To ensure the reliability and the accuracy of the results, two authors independently uploaded the data into the statistical software programs and verified that the results were identical.

RESULTS

Characteristics of included studies

Among the 60 initially identified studies with potential relevance, 24 were excluded based on the study population having: spontaneous clearance of HCV ($n = 6$[28–33]); HIV co-infection ($n = 6$[34–39]); liver transplant ($n = 6$[40–45]); decompensated liver cirrhosis or HCC ($n = 3$[46–48]); treatment with non-PEG IFN ($n = 1$[49]); and no SVR data for IL28B rs12979860 or rs8099917 polymorphisms ($n = 2$[50, 51]). In addition, 11 articles were excluded for being: reviews ($n = 10$[52–61]); and an earlier publication of a multi-published trial ($n = 1$[28]). Consequently, eight studies[62–69] evaluated IL28B rs12979860 genotype CC vs. CT/TT only, eight studies[19, 21, 22, 70–74] evaluated rs8099917 TT vs. TG/GG only, and nine studies[75–83] evaluated IL28B rs12979860 genotype CC and rs8099917 genotype TT simultaneously. In total, 25 studies[19, 21, 22, 62–83] evaluating IL28B rs12979860 genotype CC ($n = 17$; 4252 cases) and rs8099917 genotype TT ($n = 17$; 4549 cases) were included in the meta-analyses (Figure 1).

The main characteristics of these studies are presented in Table 1. In all studies, HCV genotype 1/4-infected patients received subcutaneous PEG IFN-α-2a (180 μg/week) or PEG IFN-α-2b (1.5 μg/kg/week) and oral RBV (according to body weight) for 48 weeks, and HCV genotype 2/3-infected patients received subcutaneous PEG IFN and oral RBV for 24 weeks.

Meta-analyses results

For IL28B rs12979860, the between-study heterogeneity was significant when all 17 studies were pooled for analysis ($I^2 = 79\%$, $P < 0.001$); thus, the random-effects model was used. The pooled results indicated that IL28B rs12979860 genotype CC was associated with SVR in PEG IFN-α/RBV-treated HCV patients (OR = 4.76, 95% CI: 3.15–7.20; Figure 2a). Virus genotype stratification analyses indicated that rs12979860 CC was associated with SVR in HCV patients infected with genotypes 1 or 4 ($OR_{genotype\ 1} = 5.52$, 95% CI: 3.74–8.15; $OR_{genotype\ 4} = 8.11$, 95% CI: 4.13–15.93; Figure 2b and d respectively). No association was found for genotype 2/3 ($OR_{genotype\ 2/3} = 1.23$, 95% CI: 0.71–2.14; Figure 2c). Ethnicity stratification analysis of genotype 1 showed that rs12979860 CC was associated with SVR in Asians, Caucasians and Africans ($OR_{Asians} = 5.79$, 95% CI: 2.42–12.22; $OR_{Caucasians} = 5.48$, 95% CI: 3.34–9.01; $OR_{Africans} = 5.43$, 95% CI: 2.70–10.92; Table 2). Since the genotype 2/3 and genotype 4 sub-groups had smaller sample sizes and were primarily composed of Caucasians, ethnicity stratification analyses were not performed.

For IL-28B rs8099917, the between-study heterogeneity was significant when all 17 studies were pooled for meta-analysis ($I^2 = 77\%$, $P < 0.001$); thus, the random-effects model was used. The pooled results indicated that rs8099917 TT was associated with SVR in PEG IFN-α-treated HCV patients (OR = 3.31, 95% CI: 2.39–4.59; Figure 3a). In genotype 1 stratification analysis, rs8099917 TT was also associated with SVR in HCV patients (OR = 4.28, 95% CI: 2.87–6.38; Figure 3b). In the ethnicity stratification analysis for genotype 1, the association remained for Asians and Caucasians ($OR_{Asians} = 8.09$, 95% CI: 5.63–11.61; $OR_{Caucasians} = 3.00$, 95% CI:

© 2012 Blackwell Publishing Ltd

Table 1 | Characteristics of IL28B rs12979860 and rs8099917 polymorphisms' genotype distributions in studies included in the meta-analysis

						Genotype for patients			Genotype for SVR	
IL28B polymorphism	No.	Reference	HCV genotype	Ethnicity (region)	No. of patients	CC (TT)	CT/TT (TG/GG)	No. of SVR	CC (TT)	CT/TT (TG/GG)
rs12979860	1	Thompson *et al.*[62]	1	Caucasian, African (US)	1587	512	1075	639	340	299
				Caucasian,	1287	470	817	582	320	262
				African	300	42	258	57	20	37
	2	McCarthy *et al.*[63]	1, 2, 3	Caucasian, African (US)	231	76	155	72	43	29
	3	Mangia *et al.*[64]	2/3	Caucasian (Italy)	268	100	168	201	82	119
	4	Lagging *et al.*[75]	1	Caucasian (Europe)	168	44	124	88	29	59
	5	Stattermayer *et al.*[76]	1, 2, 3, 4	Caucasian (Austria)	682	250	432	426	201	225
			1		372	129	243	208	102	105
			2/3		208	87	121	160	70	90
			4		102	34	68	59	29	30
	6	Halfon *et al.*[77]	1, 2, 3	Caucasian (Israel)	198	61	137	108	44	64
			1		156	46	110	77	32	45
			2/3		42	15	27	31	12	19
	7	Lindh *et al.*[78]	1	Caucasian (Sweden)	110	28	82	37	24	13
	8	Lin *et al.*[79]	1	Asian (Taiwan)	191	171	20	131	124	7
	9	Liao *et al.*[65]	1, 2, 3, 6	Asian (China)	92	82	10	58	56	2
	10	Moghaddam *et al.*[80]	3	Caucasian (Norway)	281	129	152	226	99	127
	11	De Nicola *et al.*[66]	4	Caucasian, African (Italy)	103	24	79	50	21	29
	12	Asselah *et al.*[67]	4	Caucasian, African (France)	82	22	60	43	18	25
	13	Venegas *et al.*[81]	1	Caucasian (Chile)	99	20	79	50	19	31
	14	Lyoo *et al.*[82]	1	Asian (Korea)	65	57	8	42	40	2
	15	Arends *et al.*[68]	1, 4	Caucasian (Netherlands)	13	6	7	6	5	1
	16	Alestig *et al.*[69]	1	Caucasian (Sweden)	50	18	32	29	16	13
	17	Honda *et al.*[83]	1	Asian (Japan)	32	18	14	15	12	3
rs8099917	1	Tanaka *et al.*[19]	1	Asian (Japan)	314	196	118	140	125	15
	2	Suppiah *et al.*[21]	1	Caucasian (Australia)	848	442	406	392	247	145
	3	Rauch *et al.*[22]	1, 2, 3, 4	Caucasian (Switzerland)	465	272	193	297	201	96
	4	Lagging *et al.*[75]	1	Caucasian (Europe)	168	97	71	88	54	34
	5	Stattermayer *et al.*[76]	1, 2, 3, 4	Caucasian (Austria)	682	409	273	426	289	137
			1		372	219	153	207	148	59
			2/3		208	118	90	160	95	65
			4		102	72	30	59	46	13
	6	Halfon *et al.*[77]	1, 2, 3	Caucasian (Israel)	198	115	83	108	73	35
			1		156	85	71	77	51	26
			2/3		42	30	12	31	22	9
	7	Lindh *et al.*[78]	1	Caucasian (Sweden)	110	66	44	63	50	13
	8	Lin *et al.*[79]	1	Asian (Taiwan)	191	170	21	131	123	8
	9	Moghaddam *et al.*[80]	3	Caucasian (Norway)	281	201	80	226	161	65
	10	Venegas *et al.*[81]	1	Caucasian (Chile)	99	29	70	50	25	25
	11	Lyoo *et al.*[82]	1	Asian (Korea)	65	56	9	42	39	3
	12	Ridruejo *et al.*[70]	1	Caucasian (Argentina)	102	41	61	37	20	17
	13	Hashimoto *et al.*[71]	1	Asian (Japan)	84	63	21	43	38	5
	14	Sakamoto *et al.*[72]	2	Asian (Japan)	129	100	29	98	81	17
	15	Yu *et al.*[73]	2	Asian (Taiwan)	482	432	50	429	386	43
	16	Hayashi *et al.*[74]	1	Asian (Japan)	299	219	80	138	127	11
	17	Honda *et al.*[83]	1	Asian (Japan)	32	18	14	15	12	3

© 2012 Blackwell Publishing Ltd

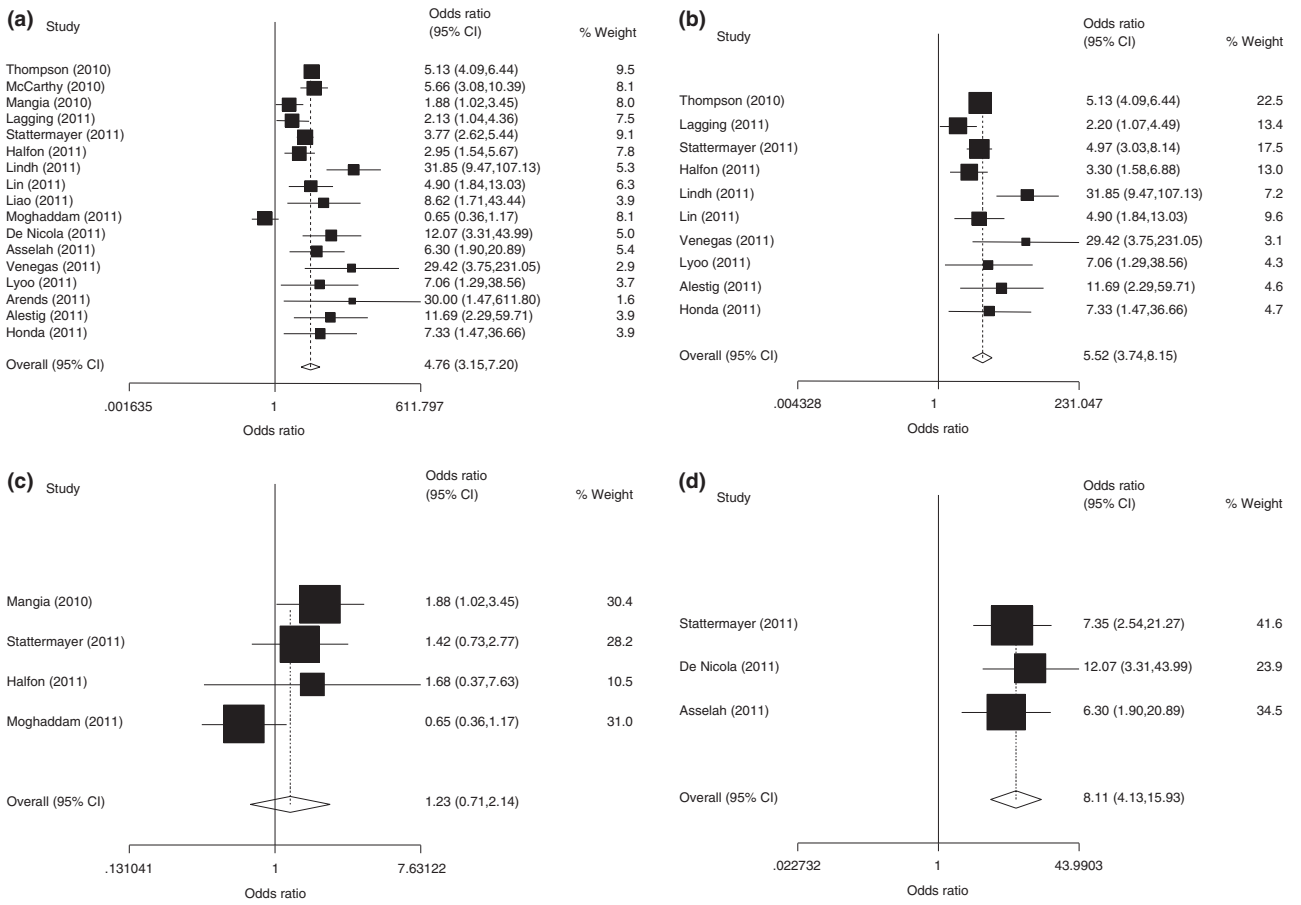

Figure 2 | Association of IL28B rs12979860 genotype CC and SVR in PEG IFN-α/RBV-treated HCV patients, compared to genotype CT/TT. Random-effects model-forest plots of pooled ORs with 95% CI are shown for (a) total pooled analysis, (b) studies evaluating genotype 1 and (c) studies evaluating genotype 2/3. Fixed- effects model-forest plot of pooled ORs with 95% CI is shown for (d) studies evaluating genotype 4.

2.03–4.45). In genotype 2/3 stratification analysis, however, rs8099917 genotype TT was not associated with SVR in HCV patients (OR = 1.40, 95% CI: 0.98–2.00; Figure 3c). Ethnicity stratification analysis of genotype 2/3 found no association among Caucasians (OR = 1.19, 95% CI: 0.77–1.84), but did find association among Asians (OR = 1.99, 95% CI: 1.09–3.62) (Figure 3d and Table 2).

Heterogeneity analysis

For IL28B rs12979860, the between-study heterogeneity was not only significant for the pooled analyses (n = 17), but also for the virus genotype stratification analyses (genotype 1: $P = 0.020$, $I^2 = 54\%$; genotype 2/3: $P = 0.085$, $I^2 = 55\%$). Furthermore, ethnicity stratification analysis of patients with genotype 1 indicated that the between-study heterogeneity was significant for Caucasians ($P = 0.003$, $I^2 = 69\%$), but was not significant for the Asians or Africans (Table 2). In addition, Galbraith plotting of all 17 studies identified two outliers[78, 80] as possible sources of heterogeneity (Figure 4a). Galbraith plotting of patients with genotype 1 identified one study[78] as an outlier (Figure 4b), and it was one of the two previously identified for the Caucasians (Figure 4c). Excluding these two outlier studies did not significantly adjust the pooloed heterogeneity ($P < 0.10$). Genotype 1 stratification analysis with the corrected pool (heterogeneity source[78] removed) indicated that heterogeneity was adjusted and reduced ($P = 0.229$, $I^2 = 24\%$). Caucasian stratification analysis with the corrected pool, however, indicated that heterogeneity was not significantly adjusted ($P = 0.091$, $I^2 = 47\%$).

For IL-28B rs8099917, the between-study heterogeneity was not only significant for the pooled analysis (n = 17), but also for the virus genotype stratification

© 2012 Blackwell Publishing Ltd

Table 2 | Summary of IL28B polymorphism influence on SVR in PEG IFN-α/RBV-treated HCV patients in this meta-analysis

IL28B polymorphism	Major genotype vs. minor genotype*	No. of studies	Odds ratio			Heterogeneity			Begg's test, *P*	Egger's test, *P*
			OR [95% CI]	*P*	M†	Q	I^2 (%)	*P*‡		
rs12979860	Overall	17	4.76 [3.15, 7.20]	<0.001	R	75.45	79	<0.001	0.077	0.450
	Overall with adjustment for heterogeneity¶	15	4.49 [3.37, 5.98]	<0.001	R	26.28	47	0.024	0.075	0.312
	Genotype 1	10	5.52 [3.74, 8.15]	<0.001	R	19.61	54	0.020	0.074	0.336
	Genotype 1 with adjustment for heterogeneity**	9	4.92 [4.10, 5.91]	<0.001	F	10.55	24	0.229	0.175	0.644
	Ethnicity stratification analysis									
	Asians	3	5.79 [2.42, 12.22]	<0.001	F	0.25	0	0.884	1.000	0.095
	Caucasians	7	5.48 [3.34, 9.01]	<0.001	R	19.56	69	0.003	0.230	0.306
	Caucasians with adjustment for heterogeneity**	6	4.30 [2.95, 6.26]	<0.001	R	9.50	47	0.091	0.260	0.645
	Africans	1	5.43[2.70, 10.92]	<0.001	F	-§	-§	-§	-§	-§
	Genotype 2/3, for all Caucasians	4	1.23 [0.71, 2.14]	0.455	R	6.63	55	0.085	1.000	0.755
	Genotype 4	3	8.11 [4.13, 15.93]	<0.001	F	0.57	0	0.753	1.000	0.587
IL-28B rs8099917	Overall	17	3.31 [2.39, 4.59]	<0.001	R	68.41	77	<0.001	0.053	0.146
	Genotype 1	13	4.28 [2.87, 6.38]	<0.001	R	50.21	76	<0.001	0.161	0.074
	Genotype 1 with adjustment for heterogeneity ††	9	3.89 [2.99, 5.07]	<0.001	F	9.41	15	0.309	0.076	0.099
	Ethnicity stratification analysis									
	Asians	6	8.09 [5.63, 11.61]	<0.001	F	4.81	0	0.439	0.707	0.121
	Caucasians	7	3.00 [2.03, 4.45]	<0.001	R	18.21	67	0.006	0.133	0.235
	Caucasians with adjustment for heterogeneity‡‡	5	2.38 [1.95, 2.91]	<0.001	F	5.59	28	0.232	1.000	0.857
	Genotype 2/3	5	1.40 [0.98, 2.00]	0.062	F	4.75	16	0.314	1.000	0.914
	Ethnicity stratification analysis									
	Asians	2	1.99 [1.09, 3.62]	0.024	F	1.57	36	0.210	1.000	-§
	Caucasians	3	1.19 [0.77, 1.84]	0.438	F	1.42	0	0.493	1.000	0.796

HCV, hepatitis C virus; IL 28B, interleukin 28B; PEG IFN-α pegylated interferon-alpha; SVR, single nucleotide polymorphisms.

* Comparison of IL28B rs12979860 genotype CC with genotype CT/TT or comparison of IL28B rs8099917 genotype TT with genotype TG/GG.

† M, model of meta-analysis: R, random-effects model; F, fixed-effects model.

‡ *P*, the *P*-value of heterogeneity.

§ Values could not be calculated.

¶ Adjustment for heterogeneity was performed by excluding the outlier studies (potential soures of heterogeneity) from Lindh *et al.* and Moghaddam *et al.*

** Adjustment for heterogeneity was performed by excluding the outlier study from Lindh *et al.*

†† Adjustment for heterogeneity was performed by excluding the outlier studies from Tanaka *et al.*, Suppiah *et al.*, Lagging *et al.* and Hayashi *et al.*

‡‡ Adjustment for heterogeneity was performed by excluding the outlier studies from Lindh *et al.* and Venegas *et al.*

© 2012 Blackwell Publishing Ltd

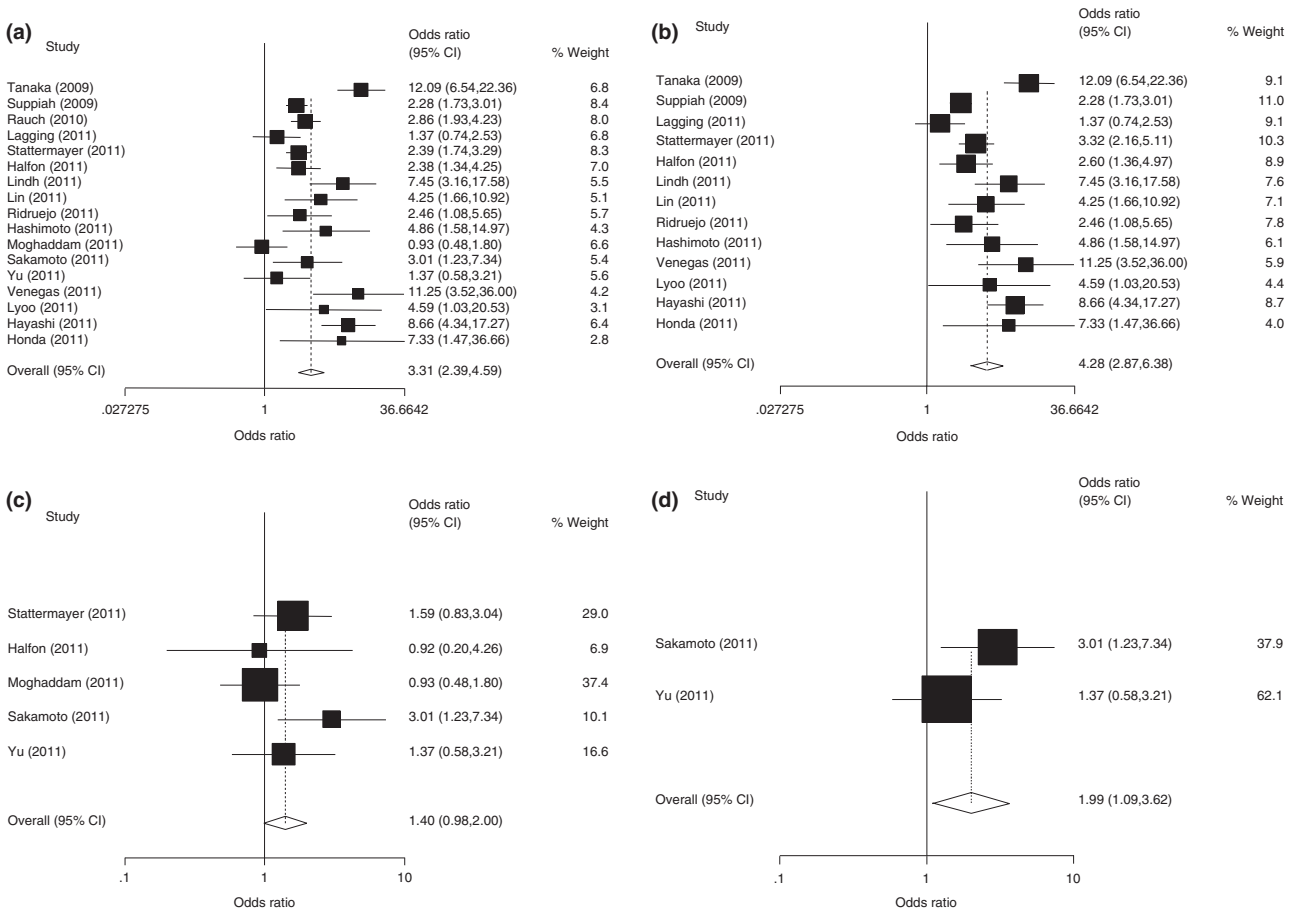

Figure 3 | Association of IL28B rs8099917 genotype TT and SVR in PEG IFN-α/RBV -treated HCV patients, compared to genotype TG/GG. Random-effects model-forest plots of pooled ORs with 95% CI are shown for (a) total pooled studies and (b) studies evaluating genotype 1. Fixed-effects model-forest plots of pooled ORs with 95% CI are shown for (c) studies evaluating genotype 2/3 and (d) Asian ethnicity stratification analysis for genotype 2/3.

analysis of genotype 1 ($P < 0.001$, $I^2 = 77\%$). In contrast, heterogeneity was not significant for genotype 2/3 ($P = 0.314$, $I^2 = 16\%$). In patients with genotype 1, the between-study heterogeneity was significant for ethnicity stratification analysis of Caucasians ($P = 0.006$, $I^2 = 67\%$), but not for any of the other ethnicities. In addition, Galbraith plotting of the overall pooled studies ($n = 17$) identified five outliers[19, 74, 78, 80, 81] as potential sources of heterogeneity (Figure 4d). Galbraith plotting of patients with genotype 1 identified four studies as outliers (Figure 4e), while plotting of Caucasian patients with genotype 1 identified two studies (Figure 4f). Exclusion of the four heterogeneity sources[19, 21, 74, 75] adjusted and reduced the heterogeneity for patients with genotype 1 ($P = 0.309$, $I^2 = 15\%$), as did removal of the two sources[78, 81] from the Caucasian genotype 1 analysis ($P = 0.232$, $I^2 = 28\%$). We did not try to reduce the obvious between-study heterogeneity of the overall analyses ($n = 17$) because it would have required excluding five studies (35%) and may have caused bias.

Sensitivity analysis

Sensitivity analysis was performed by sequential omission of individual studies. For pooled analyses of more than three individual studies, the significance of ORs was not influenced excessively by omitting any single study (data not shown). For the IL28B rs12979860 polymorphism in overall populations ($n = 17$), the two outlier studies[78, 80] from Galbraith plotting were removed and the significance of OR was not altered. Sensitivity analysis in patients with genotype 1 was performed by omitting the Galbraith plotting outlier study,[78] and the significance of ORs were not altered (Table 2). For the IL28B rs8099917 polymorphism in overall populations ($n = 17$), sensitivity analysis was not performed because too many studies ($n = 5$) would have to be excluded. However, sensitivity analysis was

© 2012 Blackwell Publishing Ltd

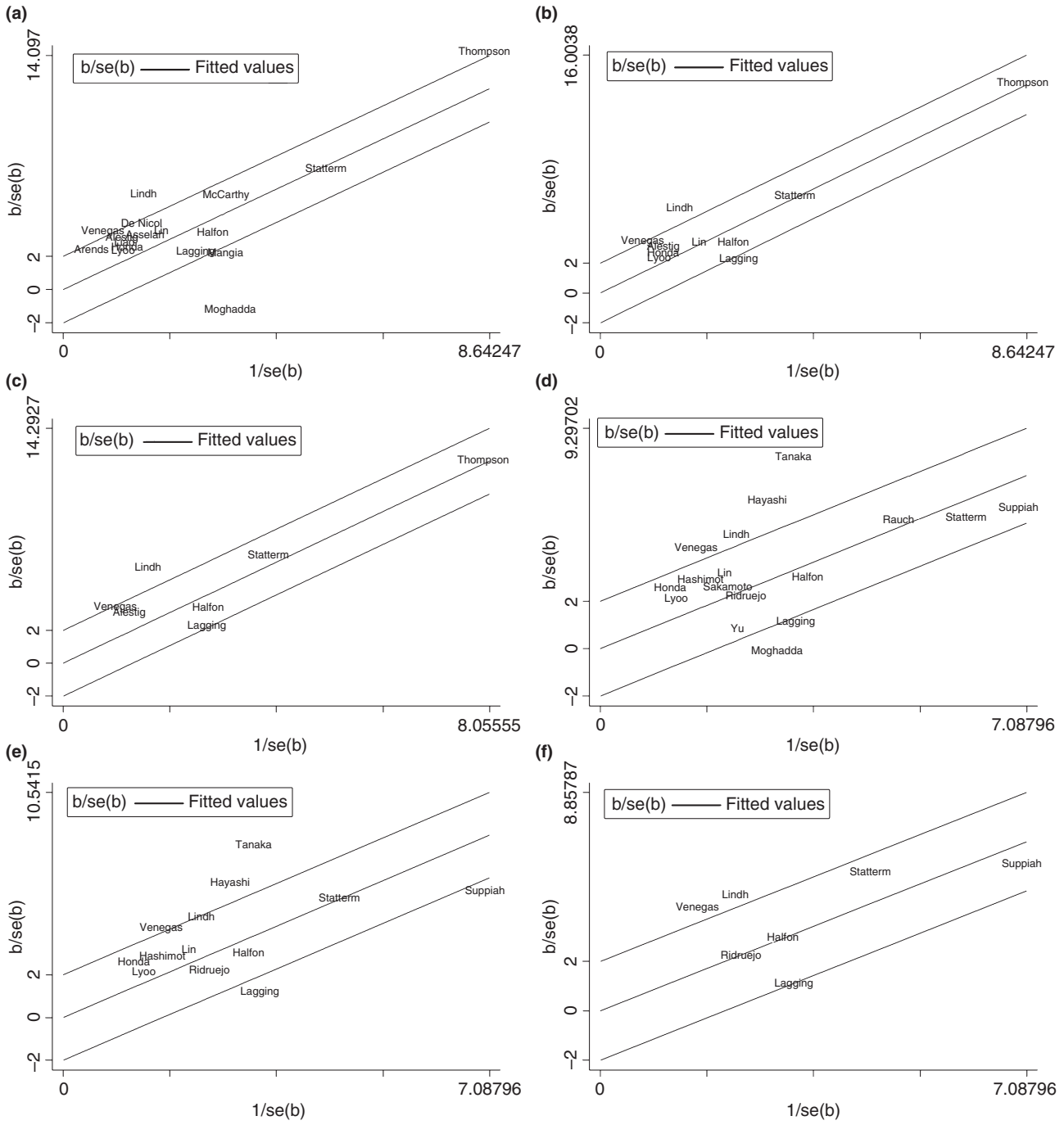

Figure 4 | Identification of studies acting as sources of heterogeneity for the associations between IL28B polymorphisms and SVR in PEG IFN-α/RBV-treated HCV patients. Each author listed represents a separate study (shown in Tables 1 and 2) for the indicated association. Galbraith plots of the associations between IL28B (a, b, c) rs12979860 or (d, e, f) rs8099917 polymorphism genotype and SVR in (a, d) overall populations, (b, e) all genotype 1 patients, (c, f) Caucasian genotype 1 patients.

performed for patients with genotype 1 by omitting the four Galbraith plotting outlier studies,[19, 21, 74, 75] and for Caucasian patients with genotype 1 by omitting the two Galbraith plotting outlier studies[67, 78]; for each, the significance of ORs were not altered (Table 2).

Publication bias

Begg's test and Egger's test were performed to access the publication bias in this meta-analysis. Funnel plot shapes did not reveal obvious evidence of asymmetry and the *P*-values of both Begg's and Egger's tests were >0.05

© 2012 Blackwell Publishing Ltd

(Table 2), providing statistical evidence of the funnel plots' symmetry. Thus, publication bias was not evident in this meta-analysis.

DISCUSSION

Recent GWAS have identified genetic variations near the IL28B gene that are strongly associated with spontaneous and treatment-induced clearance of HCV infection. IL28B variations have been reported as strongly associated with on- treatment viral kinetics and with ~twofold increased SVR rates in HCV genotype 1 and in four patients. In fact, IL28B variations were shown to be the strongest pre-treatment predictor of virological response in HCV genotype 1 patients, but ineffective predictors for genotype 2/3-infected patients.[56] Variations in IL28B may also influence the kinetics of viral response to therapy. In one study, PEG-IFN/RBV-treated patients carrying the rs12979860 CC genotype had a greater HCV RNA decline than patients with the CT or TT genotype.[62] IL28B rs12979860 has also been associated with liver fibrosis in chronic HCV infection. In particular, the T allele affects the severity of fibrosis.[47] In our meta-analysis, pooled analysis of all studies showed that both rs12979860 CC and rs8099917 TT were associated with SVR in PEG IFN-α/RBV- treated HCV patients. Genotype stratification analyses showed that rs12979860 CC and rs8099917 TT were both associated with SVR in genotype 1, and not genotype 2/3, HCV patients. Ethnicity stratification analyses of genotype 1 patients showed that rs12979860 CC and rs8099917 TT were both associated with SVR in Asians, Caucasians and Africans. Thus, for genotype 1-infected patients, tests for IL28B rs12979860 or rs8099917 polymorphisms may help guide the physician in treatment regimen and design and/or the patient's decision to undergo therapy. In the ethnicity stratification analyses for genotype 2/3-infected patients, rs12979860 CC was not associated with SVR in Asians or Caucasians, but rs8099917 TT was associated with SVR in Asians.

It should be noted when interpreting the findings from our study that the meta-analysis design used has some possible limitations. First, meta-analyses are most powerful when performed with all available individual patient data, including data from trials that have not been published. In our meta-analysis, only published studies were included. As such, publication bias may have occurred, even though Begg's test and Egger's test were performed to access the publication bias and indicated no such bias existed. Second, the genotype 2/3 and genotype 4 groups were relatively small in size, and this may impact the generalisability of our conclusions. Future studies with larger groups of genotype 2/3 and genotype 4 patients, including those from different ethnicities, should be conducted to validate the associations with IL28B polymorphisms. Third, meta-analysis is an observational study that is subject to methodological deficiencies of the included studies. Fourth, the amount of published studies on genotype 2/3 and genotype 4 patients were insufficient to conduct ethnicity stratification analysis. Finally, it is very likely that non-genetic factors, such as viral load at treatment initiation and patient physical and physiological features, may influence SVR of antiviral-treated chronic HCV patients; however, very limited data on such potential factors were reported in the studies included in our analysis.

Nonetheless, our meta-analysis suggests that both IL28B rs12979860 CC and rs8099917 TT genotypes are strong predictors of SVR in PEG IFN-α/RBV-treated HCV genotype 1-infected patients, regardless of ethnicity. In contrast, rs12979860 CC has no predictive impact of SVR in genotype 2/3-infected patients, but rs8099917 TT is slightly associated with SVR in genotype 2/3-infected Asians.

ACKNOWLEDGEMENTS

Declaration of personal interests: None. *Declaration of funding interests*: This study was funded in full by the Major National Science and Technology Projects for Infectious Diseases (11th Five-Year Plan, China) (2008ZX10002-007), the National Natural Science Fund of China (Project Number 30872219) and Jiangsu Health International Exchange Program sponsorship (JSH-2011-051).

REFERENCES

1. EASL. Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**: 245–64.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.
3. Manns MP, McHutchison JG, Gordon SC, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.
4. Fried MW, Shiffman ML, Reddy KR, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus

© 2012 Blackwell Publishing Ltd

infection. *N Engl J Med* 2002; **347**: 975–82.
5. Jacobson IM, Brown RS Jr, Freilich B, *et al.* Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007; **46**: 971–81.
6. Liu CH, Liu CJ, Lin CL, *et al.* Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin Infect Dis* 2008; **47**: 1260–9.
7. Yu ML, Dai CY, Huang JF, *et al.* Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology* 2008; **47**: 1884–93.
8. McHutchison JG, Lawitz EJ, Shiffman ML, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; **361**: 580–93.
9. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology* 2002; **36**: S237–44.
10. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008; **49**: 634–51.
11. Asselah T, Estrabaud E, Bieche I, *et al.* Hepatitis C: viral and host factors associated with non-response to pegylated interferon plus ribavirin. *Liver Int* 2010; **30**: 1259–69.
12. Khattab M, Eslam M, Sharwae MA, Shatat M, Ali A, Hamdy L. Insulin resistance predicts rapid virologic response to peginterferon/ribavirin combination therapy in hepatitis C genotype 4 patients. *Am J Gastroenterol* 2010; **105**: 1970–7.
13. Ramcharran D, Wahed AS, Conjeevaram HS, *et al.* Associations between serum lipids and hepatitis C antiviral treatment efficacy. *Hepatology* 2010; **52**: 854–63.
14. Harrison SA, Rossaro L, Hu KQ, *et al.* Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. *Hepatology* 2010; **52**: 864–74.
15. Bitetto D, Fattovich G, Fabris C, *et al.* Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. *Hepatology* 2011; **53**: 1118–26.
16. Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med* 2004; **350**: 2265–71.
17. Romero-Gomez M, Gonzalez-Escribano MF, Torres B, *et al.* HLA class I B44 is associated with sustained response to interferon + ribavirin therapy in patients with chronic hepatitis C. *Am J Gastroenterol* 2003; **98**: 1621–6.
18. Yee LJ, Tang J, Gibson AW, Kimberly R, Van Leeuwen DJ, Kaslow RA. Interleukin 10 polymorphisms as predictors of sustained response in antiviral therapy for chronic hepatitis C infection. *Hepatology* 2001; **33**: 708–12.
19. Tanaka Y, Nishida N, Sugiyama M, *et al.* Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105–9.
20. Ge D, Fellay J, Thompson AJ, *et al.* Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399–401.
21. Suppiah V, Moldovan M, Ahlenstiel G, *et al.* IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100–4.
22. Rauch A, Kutalik Z, Descombes P, *et al.* Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010; **138**: 1338–45.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
24. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719–48.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
26. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. *Stat Med* 1988; **7**: 889–94.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.
28. Thomas DL, Thio CL, Martin MP, *et al.* Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009; **461**: 798–801.
29. di Iulio J, Ciuffi A, Fitzmaurice K, *et al.* Estimating the net contribution of interleukin-28B variation to spontaneous hepatitis C virus clearance. *Hepatology* 2011; **53**: 1446–54.
30. Tillmann HL, Thompson AJ, Patel K, *et al.* A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology* 2010; **139**: 1586–92, 1592 e1581.
31. Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA, *et al.* Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. *Hepatology* 2011; **53**: 1830–8.
32. Knapp S, Warshow U, Ho KM, *et al.* A polymorphism in IL28B distinguishes exposed, uninfected individuals from spontaneous resolvers of HCV infection. *Gastroenterology* 2011; **141**: 320–5.
33. Montes-Cano MA, Garcia-Lozano JR, Abad-Molina C, *et al.* Interleukin-28B genetic variants and hepatitis virus infection by different viral genotypes. *Hepatology* 2010; **52**: 33–7.
34. Pineda JA, Caruz A, Rivero A, *et al.* Prediction of response to pegylated interferon plus ribavirin by IL28B gene variation in patients coinfected with HIV and hepatitis C virus. *Clin Infect Dis* 2010; **51**: 788–95.
35. Nattermann J, Vogel M, Nischalke HD, *et al.* Genetic variation in IL28B and treatment-induced clearance of hepatitis C virus in HIV-positive patients with acute and chronic hepatitis C. *J Infect Dis* 2011; **203**: 595–601.
36. Clausen LN, Weis N, Astvad K, *et al.* Interleukin-28B polymorphisms are associated with hepatitis C virus clearance and viral load in a HIV-1-infected cohort. *J Viral Hepat* 2011; **18**: e66–74.
37. Rallon NI, Naggie S, Benito JM, *et al.* Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. *AIDS* 2010; **24**: F23–9.
38. Rallon NI, Soriano V, Naggie S, *et al.* IL28B gene polymorphisms and viral kinetics in HIV/hepatitis C virus-coinfected patients treated with pegylated interferon and ribavirin. *AIDS* 2011; **25**: 1025–33.
39. Neukam K, Nattermann J, Rallon N, *et al.* Different distributions of hepatitis C virus genotypes among HIV-infected patients with acute and chronic hepatitis C according to interleukin-28B genotype. *HIV Med* 2011; **12**: 487–93.
40. Charlton MR, Thompson A, Veldt BJ, *et al.* Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology* 2011; **53**: 317–24.
41. Coto-Llerena M, Perez-Del-Pulgar S, Crespo G, *et al.* Donor and recipient IL28B polymorphisms in HCV-infected patients undergoing antiviral therapy before and after liver transplantation. *Am J Transplant* 2011; **11**: 1051–7.
42. Eurich D, Boas-Knoop S, Ruehl M, *et al.* Relationship between the

© 2012 Blackwell Publishing Ltd

interleukin-28b gene polymorphism and the histological severity of hepatitis C virus-induced graft inflammation and the response to antiviral therapy after liver transplantation. *Liver Transpl* 2011; **17**: 289–98.
43. McCaughan GW, Shackel NA, Bowen DG. Liver transplantation and hepatitis C: will understanding the interleukin-28B polymorphisms improve outcomes? *Liver Transpl* 2011; **17**: 219–21.
44. Neumann U. Impact of IL-28B polymorphism on outcome in patients with hepatitis C after liver transplantation. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 429–31.
45. Lange CM, Moradpour D, Doehring A, *et al.* Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. *J Hepatol* 2011; **55**: 322–7.
46. Fabris C, Falleti E, Cussigh A, *et al.* IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC. *J Hepatol* 2011; **54**: 716–22.
47. Falleti E, Bitetto D, Fabris C, *et al.* Role of interleukin 28B rs12979860 C/T polymorphism on the histological outcome of chronic hepatitis C: relationship with gender and viral genotype. *J Clin Immunol* 2011; **31**: 891–9.
48. Kawaoka T, Aikata H, Takaki S, *et al.* IL28B polymorphism may guide pegylated interferon plus ribavirin therapy even after curative treatment for hepatitis C virus-related hepatocellular carcinoma. *J Viral Hepat* 2011; **18**: e550–60.
49. Akuta N, Suzuki F, Hirakawa M, *et al.* Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology* 2010; **52**: 421–9.
50. Sugiyama M, Tanaka Y, Wakita T, Nakanishi M, Mizokami M. Genetic variation of the IL-28B promoter affecting gene expression. *PLoS One* 2011; **6**: e26620.
51. Cariani E, Critelli R, Rota C, Luongo M, Trenti T, Villa E. Interleukin 28B genotype determination using DNA from different sources: a simple and reliable tool for the epidemiological and clinical characterization of hepatitis C. *J Virol Methods* 2011; **178**: 235–8.
52. Balagopal A, Thomas DL, Thio CL. IL28B and the control of hepatitis C virus infection. *Gastroenterology* 2010; **139**: 1865–76.
53. Afdhal NH, McHutchison JG, Zeuzem S, *et al.* Hepatitis C pharmacogenetics: state of the art in 2010. *Hepatology* 2011; **53**: 336–45.
54. Tao J, Liu J, Ben KL. Role of IL-28B SNPs in the treatment and prognosis of HCV infection. *Zhonghua Gan Zang Bing Za Zhi* 2011; **19**: 316–7.
55. Clark PJ, Thompson AJ, McHutchison JG. IL28B genomic-based treatment paradigms for patients with chronic hepatitis C infection: the future of personalized HCV therapies. *Am J Gastroenterol* 2011; **106**: 38–45.
56. Lange CM, Zeuzem S. IL28B single nucleotide polymorphisms in the treatment of hepatitis C. *J Hepatol* 2011; **55**: 692–701.
57. Gonzalez SA, Keeffe EB. IL-28B as a predictor of sustained virologic response in patients with chronic hepatitis C virus infection. *Gastroenterol Hepatol (N Y)* 2011; **7**: 366–73.
58. Imazeki F, Yokosuka O, Omata M. Impact of IL-28B SNPs on control of hepatitis C virus infection: a genome-wide association study. *Expert Rev Anti Infect Ther* 2010; **8**: 497–9.
59. Pearlman BL. The IL-28 genotype: how it will affect the care of patients with hepatitis C virus infection. *Curr Gastroenterol Rep* 2011; **13**: 78–86.
60. Sugiyama M, Tanaka Y, Nakanishi M, Mizokami M. Novel findings for the development of drug therapy for various liver diseases: genetic variation in IL-28B is associated with response to the therapy for chronic hepatitis C. *J Pharmacol Sci* 2011; **115**: 263–9.
61. Cariani E, Villa E, Rota C, Critelli R, Trenti T. Translating pharmacogenetics into clinical practice: interleukin (IL) 28B and inosine triphosphatase (ITPA) polymophisms in hepatitis C virus (HCV) infection. *Clin Chem Lab Med* 2011; **49**: 1247–56.
62. Thompson AJ, Muir AJ, Sulkowski MS, *et al.* Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010; **139**: 120–9.
63. McCarthy JJ, Li JH, Thompson A, *et al.* Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. *Gastroenterology* 2010; **138**: 2307–14.
64. Mangia A, Thompson AJ, Santoro R, *et al.* An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology* 2010; **139**: 821–7.
65. Liao XW, Ling Y, Li XH, *et al.* Association of genetic variation in IL28B with hepatitis C treatment-induced viral clearance in the Chinese Han population. *Antivir Ther* 2011; **16**: 141–7.
66. De Nicola S, Aghemo A, Rumi MG, *et al.* An IL28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis c genotype 4. *Hepatology* 2012; **55**: 336–42.
67. Asselah T, De Muynck S, Broet P, *et al.* IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol* 2012; **56**: 527–32.
68. Arends JE, Fransen JH, Hoepelman AI, van Baarle D. Association between IL28B polymorphisms and first-phase viral load decrease in chronic hepatitis C virus-infected patients treated with peginterferon alfa-2b/ribavirin. *Int J Antimicrob Agents* 2011; **38**: 538–9.
69. Alestig E, Arnholm B, Eilard A, *et al.* Core mutations, IL28B polymorphisms and response to peginterferon/ribavirin treatment in Swedish patients with hepatitis C virus genotype 1 infection. *BMC Infect Dis* 2011; **11**: 124.
70. Ridruejo E, Solano A, Marciano S, *et al.* Genetic variation in Interleukin-28B predicts SVR in hepatitis C genotype 1 Argentine patients treated with PEG IFN and ribavirin. *Ann Hepatol* 2011; **10**: 452–7.
71. Hashimoto Y, Ochi H, Abe H, *et al.* Prediction of response to peginterferon-alfa-2b plus ribavirin therapy in Japanese patients infected with hepatitis C virus genotype 1b. *J Med Virol* 2011; **83**: 981–8.
72. Sakamoto N, Nakagawa M, Tanaka Y, *et al.* Association of IL28B variants with response to pegylated-interferon alpha plus ribavirin combination therapy reveals intersubgenotypic differences between genotypes 2a and 2b. *J Med Virol* 2011; **83**: 871–8.
73. Yu ML, Huang CF, Huang JF, *et al.* Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology* 2011; **53**: 7–13.
74. Hayashi K, Katano Y, Honda T, *et al.* Association of interleukin 28B and mutations in the core and NS5A region of hepatitis C virus with response to peg-interferon and ribavirin therapy. *Liver Int* 2011; **31**: 1359–65.
75. Lagging M, Askarieh G, Negro F, *et al.* Response prediction in chronic hepatitis C by assessment of IP-10 and IL28B-related single nucleotide polymorphisms. *PLoS ONE* 2011; **6**: e17232.
76. Stattermayer AF, Stauber R, Hofer H, *et al.* Impact of IL28B genotype on the early and sustained virologic response

© 2012 Blackwell Publishing Ltd

in treatment-naive patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2011; **9**: 344–50.
77. Halfon P, Bourliere M, Ouzan D, *et al.* A single IL28B genotype SNP rs12979860 determination predicts treatment response in patients with chronic hepatitis C Genotype 1 virus. *Eur J Gastroenterol Hepatol* 2011; **23**: 931–5.
78. Lindh M, Lagging M, Arnholm B, *et al.* IL28B polymorphisms determine early viral kinetics and treatment outcome in patients receiving peginterferon/ribavirin for chronic hepatitis C genotype 1. *J Viral Hepat* 2011; **18**: e325–31.
79. Lin CY, Chen JY, Lin TN, *et al.* IL28B SNP rs12979860 is a critical predictor for on-treatment and sustained virologic response in patients with hepatitis C virus genotype-1 infection. *PLoS One* 2011; **6**: e18322.
80. Moghaddam A, Melum E, Reinton N, *et al.* IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. *Hepatology* 2011; **53**: 746–54.
81. Venegas M, Villanueva RA, Gonzalez K, Brahm J. IL28B polymorphisms associated with therapy response in Chilean chronic hepatitis C patients. *World J Gastroenterol* 2011; **17**: 3636–9.
82. Lyoo K, Song MJ, Hur W, *et al.* Polymorphism near the IL28B gene in Korean hepatitis C virus-infected patients treated with peg-interferon plus ribavirin. *J Clin Virol* 2011; **52**: 363–6.
83. Honda M, Sakai A, Yamashita T, *et al.* Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. *Gastroenterology* 2010; **139**: 499–509.

© 2012 Blackwell Publishing Ltd